UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/811,130	03/26/2004	Prasad Devarajan	CHM-015	2792

38155 7590 09/04/2008

HASSE & NESBITT LLC
8837 CHAPEL SQUARE DRIVE
SUITE C
CINCINNATI, OH 45249

EXAMINER	
FOSTER, CHRISTINE E	

ART UNIT	PAPER NUMBER
1641	

MAIL DATE	DELIVERY MODE
09/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/811,130	DEVARAJAN ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,9-11,30,31,33,35,37,48,52,55 and 60-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,9-11,30,31,33,35,37,48,52,55 and 60-65* is/are rejected.

7)☒ Claim(s) *1 and 30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/26/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/3/08 has been entered.

2. Claims 3, 28, 32, 34, 36, 38-40, 46-47, 49-51, 53-54, and 56-59 were canceled. New claims 60-65 have been added. Accordingly, claims 1-2, 4-5, 9-11, 30-31, 33, 35, 37, 48, 52, 55, and 60-65 are currently pending and subject to examination below.

Objections/ Rejections Withdrawn

3. The objection to the specification regarding the use of trademarks has been obviated by Applicant's amendments.

4. The rejections of claims 3, 28, 32, 34, 36, 38-40, 46-47, 49-51, 53-54, 56 and 59 are moot in light of Applicant's cancellation of these claims.

5. The rejections under § 112, 1st and 2nd paragraphs as set forth in the previous Office action have been obviated by Applicant's amendments. However, the amended claims have presented new grounds of rejection under these statutes as set forth below.

Priority

6. The present application was filed on 3/26/2004. Acknowledgment is made of applicant's claim under 35 U.S.C. 119(e) for benefit of the earlier filing dates of provisional application No. 60/458,143 (filed on 03/27/2003) and of provisional application No. 60/481,596, (filed 11/04/2003).

7. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application Nos. 60/458,143 and 60/481,596, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

The instant claims are not found to be adequately supported by the disclosure and claims as originally filed, for reasons detailed in the rejections under § 112, 1st paragraph below. For similar reasons, support could also not be found in the provisional applications. Applicant is referred to the detailed discussion below.

Specification

8. The specification is objected to for the following reasons:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1 .821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1 .821 through 1 .825 for the reason(s) set forth below.

It appears that while Applicant has successfully submitted sequences in a computer readable form, the specification is not compliant with sequence rules. **Specifically, paragraph [0072] of the instant specification refers to nucleic acid sequences that are not accompanied by SEQ ID numbers**.

If the noted sequence(s) is in the sequence listing filed, Applicants must amend the specification to identify the sequence appropriately by SEQ ID NO. If the noted sequence(s) is not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Applicant is required to review the instant application for compliance with the requirements of applications which contain sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821-1.825.

Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g).

Applicant's time to comply with the sequence rules is set forth on the attached Office Action Summary (Form PTOL-326). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned.

Claim Objections

9. Claims 1 and 30 are objected to because of the following informalities:

10. Steps (a) of the claims refer to "an event" but do not make clear that it is the subject under study that has undergone such an event, which may cause confusion. Appropriate correction is required.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-2, 4-5, 9-11, 30-31, 33, 35, 37, 48, 52, 55, and 60-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter

13. Independent claims 1 and 30, as amended in the instant Reply of 6/3/08, now recite methods for determining if a subject "**has an acute ischemic renal tubular cell injury that can progress to acute renal failure**".

The now-claimed methods encompass detection of ischemic renal tubular cell injury (i.e., methods of *diagnosis)*. However, the reference to "an acute ischemic renal tubular cell injury that can progress to acute renal failure" suggests selective determination and discrimination of those injuries that progress to ARF from those that do not progress to ARF. By invoking determining whether such an injury is one that will progress to ARF or not, the currently amended claims now encompass *prognosis* of ARF in addition to *diagnosis* of renal tubular cell injury as originally claimed. See also rejection under 112, 2nd paragraph below.

Support could not be found for such prognostic methods, in which ischemic renal tubular cell injuries that progress to ARF are selectively determined vs. those that do not progress to ARF. The methods lack clear explicit or implicit support in the disclosure as filed.

Applicant's reply indicates support at claim 56 and at paragraphs 38, 45, and 101 (Reply, pages 9-10). Support could not be found where indicated for the following reasons.

The Examiner notes that claim 56 was not present in the application as originally filed, but was added by Applicant's amendment of 11/13/07. Therefore, the claim cannot be relied upon for descriptive support for the currently amended claims.

Paragraph 101 relates the results of a specific experiment, in which human patients who had undergone open heart surgery were studied. This experiment retrospectively compared urinary NGAL levels in subjects who developed post-operative ARF with those who did not develop ARF.

By contrast, the currently presented claims are not limited to this specific patient population involving patients who had undergone open heart surgery, but encompass any mammalian subject who has experienced any "event" suspected of causing ischemic renal tubular cell injury.

In characterizing the results of the above experiment, the specification concludes that "NGAL is a novel early urinary biomarker for acute renal injury following open heart surgery, and its quantitation is predictive of acute renal failure **in this highly susceptible population**" (see conclusion of paragraph 101 at the top of page 40, emphasis added).

No generic support could be found for methods of determining if subjects have an acute ischemic renal tubular cell injury that can progress to ARF. Although the retrospective studies performed in the above experiment do appear to support prediction of ARF in the highly susceptible population of open heart surgery patients, no direction could be found in the specification to prediction or prognosis of ARF in other patient populations.

The claims, in incorporating the results of a specific experiment into the claims out of the context in which they were originally disclosed, introduce new concepts not clearly disclosed in the specification as originally filed, and therefore represent new matter.

14. In addition, claims 1 and 30 now recite obtaining urine samples from a subject "**within a period of time of about 12 hours after an event…**". Support could not be found where

indicated by Applicant (Reply, pages 9-10) for the following reasons.

No support for the currently claimed range of "within…about 12 hours" could be found in the specification. The specification does not provide generic support for methods in which urine samples are obtained **within about 12 hours** after any event suspected of causing ischemic renal tubular cell injury, e.g., kidney transplantation.

The specification does disclose the results of specific experiments in which urine samples were obtained at various time periods, including at 12 hours, following given procedures. For example, urine samples were collected from mice after induction of injury by renal artery clamping (see [0076], [0089]) and from humans after kidney transplantation or open heart surgery (see [0101] and Figure 16).

However, Applicant has now apparently incorporated this time period of "12 hours" out of the contexts in which it was originally disclosed. By incorporating this limitation of 12 hours into the claims in a generic manner, without accompanying limitations as originally disclosed, the amendments represent new matter.

In addition, the experiments disclosed in the specification involved obtaining urine samples at 12 hours, but also at various other time periods. The case of In re Ruschig (379 F.2d 990, 154 USPQ 118 (CCPA 1967)) makes clear that one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say "here is my invention." In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure. See id. at 994-95, 154 USPQ at 122; Fujikawa, 93 F.3d at 1570-71, 39 USPQ2d at 1905; Martin v. Mayer, 823 F.2d 500, 505, 3 USPQ2d 1333, 1337 (Fed. Cir. 1987) ("It is 'not a question of whether one skilled in the art might be able to

construct the patentee's device from the teachings of the disclosure. . . . Rather, it is a question whether the application necessarily discloses that particular device.'") (quoting Jepson v. Coleman, 314 F.2d 533, 536, 136 USPQ 647, 649-50 (CCPA 1963)).

In the instant case, the claims recite the range "within about 12 hours". However, in those experiments in which samples were taken **at** 12 hours, samples were also taken at a number of other time periods.

Figure 16A is illustrative: samples were obtained at 18 different time periods from 0-144 hours post bypass. There is no specific direction to the range now claimed, which would encompass time periods up to and including "about" 12 hours.

Furthermore, support could not be found for methods of sampling at "about" 12 hours. The insertion of the term "**about**" in relation to the disclosed sampling time of 12 hours broadens the scope of the claims so as to include times of 12.5 or 13 hours, for example, which are not described in the specification. Such broadening amendments, in going beyond the scope of the original disclosure, depart from the specification and claims as originally filed.

15. Claims 35 and 63-64 also present new matter for the following reasons. Claim 35 recites period of time is "**selected from the group consisting of 6 hours, 3 hours, 2 hours, 1 hour, and 30 minutes**". Similarly, newly added claims 63-64 recite that the period of time is "selected from the group consisting of 3 hours, 2 hours, 1 hour, and 30 minutes". Claim 35 was added by amendment on 11/27/07. In the accompanying Reply, Applicant indicated support at Figures 12-13 and in paragraphs 31-32. In the instant Reply, Applicant indicates support for newly added claims 63-64 in claims 1 and 35. As discussed above, claim 35 was not present in the application

as originally filed. Although claim 1 now refers to limitations involving time ("within...about 12 hours"), such limitations were presented for the first time in the instant amendment.

Paragraphs 31-32 (which refer to Figures 12-13) describe specific experiments in which cisplatin was administered to mice as a model of **nephrotoxic renal injury** (see also paragraphs 97-98). Urinary NGAL was sampled at 0, 3, 12, 24, 48, 72, and 96 hours after cisplatin administration. By contrast, the instant claims are now limited to **ischemic renal injury** and no longer read on nephrotoxic renal injury; they are also not limited to samples obtained in relation to administration of a nephrotoxic drug such as cisplatin.

The specification also discloses at [0051] that

> …a method and a kit of the present invention can detect the RTCI biomarker in a sample of urine within four hours, more typically within two hours, and most typically within one hour, following renal tubular cell injury.

Although the claimed time periods of 2 hours and 1 hour are disclosed in this passage, they are done so in relation to *renal tubular cell injury* and not in relation to "an event that predisposes the human to progressing to ARF" or to "an event that is suspected of causing an ischemic renal tubular cell injury". However, an event that predisposes or is suspected or causing ARF would not necessarily occur at the same time as the onset of renal tubular cell injury. The incorporation of the time periods out of the context in which they were originally disclosed therefore represents new matter.

16. New claims 60-61 recite that the elevated level is "at least a 10-fold increase". Applicant indicates that support may be found at [0101] and in Figure 16 (Reply, page 11). The indicated

sections refer to the results of a specific experiment that involved a particular patient population, subjects who had undergone open heart surgery. Paragraph [0101] discloses that:

> In marked contrast, patients who subsequently developed acute renal failure displayed a greater than 10-fold increase in the 2 hour value for urinary NGAL (75.+-.10 ng/mg creatinine), and a greater than 20-fold increase in the 4 hour value for urinary NGAL (120.+-.12 ng/mg creatinine).

Although in this particular experiment a 10-fold increase was in fact observed, the specification fails to disclose methods involving detection of a 10-fold increase as now claimed generically. The instant claims are not limited to patient populations such as those who were studied in this example. Furthermore, the passage above clearly refers to a 10-fold increase in urine samples "in the 2 hour value". In incorporating the words "10-fold increase" out of the context in which they were originally disclosed, the amendments introduce new concepts not clearly disclosed in the specification or claims as originally filed.

17. New claim 65 recites that "the elevated quantity of NGAL is significantly elevated above a smaller increased quantity of NGAL in a mammalian subject having an acute ischemic renal tubular cell injury that does not progress to ARF". Applicant indicates support at [0101] and Figure 16. However, as discussed above, the experiment of [0101] related to a particular patient population, while the instant claims are not so limited. In characterizing the results of that experiment, the specification discloses that "These data show that NGAL is a novel early urinary biomarker for acute renal injury ***following open heart surgery***, and its quantitation is predictive of acute renal failure ***in this highly susceptible population***" [0101]. In now characterizing the results of specific experiment relating to a specific type of injury (i.e., one caused by open heart

surgery) in a generic manner in the claims, the amendments go beyond the scope of the disclosure as originally filed.

18. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

19. Claims 1-2, 4-5, 9-11, 30-31, 33, 35, 37, 48, 52, 55, and 60-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

20. Independent claims 1 and 30 recite methods "for determining if a human has an acute ischemic renal injury that can progress to acute renal failure", which is vague and indefinite. The terminology "an...injury that **can** progress to acute renal failure" is not a positive recitation, such that it is unclear whether Applicant intends that the injury does progress to ARF or not in the subject under study. As such, the claims could be read as a diagnostic method for detecting ischemic renal injuries, and in particular that are known to in some cases progress to ARF, but with no requirement that the injuries detected actually do progress to ARF in the subjects who are diagnosed. Alternatively, the claims could be read as prognostic methods--i.e., detecting injuries and determining whether the injury is one that will progress to ARF or not. Consequently, the claims are indefinite because it is unclear whether diagnostic or prognostic methods are intended.

21. Independent claims 1 and 30 recite “an elevated quantity of NGAL” but do not make clear what the quantity of NGAL is elevated relative to, which renders the claims indefinite.

Comparison of NGAL levels with other values is suggested, but it is not apparent what the NGAL levels are being compared with.

22. The term "significantly elevated" in claim 65 is a relative term which renders the claim indefinite. The term "significantly elevated" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification does not clearly define or otherwise indicate what amount(s) would represent a "significant" elevation, such that the metes and bounds of the claim are unclear.

Claim Rejections - 35 USC § 103

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

24. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

25. Claims 5, 30, 33, 35, 37, 61, 63, and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Matthaeus et al. ("Acute Ischemic Renal Failure Induces Expression of Neutrophil Gelatinase-Associated Lipocalin and Matrix Metalloproteinase-9 in Damaged Tubuli" *Kidney Blood Press Res* (2001), Vol. 24, page 342, abstract No. P268; hereafter, "Matthaeus 1") or Matthaeus et al. ("Co-Regulation of Neutrophil Gelatinase-Associated Lipocalin and Matrix Metalloproteinase-9 in the Postischemic Rat Kidney" *J. Am Soc Nephrol* Vol. 12, September 2001, Pathophysiology of Renal Disease, pp. 787A; A4112, SUI-0348 (PS), Applicant's IDS of 11/13/07; hereafter, "Matthaeus 2" in view of Ramsden et al. (US 4,640,909), Blaser et al. ("A sandwich enzyme immunoassay for the determination of neutrophil lipocalin in body fluids" Clin Chim Acta. 1995 Mar 31;235(2):137-45, Applicant's IDS of 7/24/06), Moses et al. (US 7,153,660 B2), and Muramatsu (Kidney International, Vol. 62 (2002), pages 1601-1610, Applicant's IDS of 10/18/04; or, in the alternative, over either Matthaeus 1 or Matthaeus 2 and Ohlsson et al. ("Increased circulating levels of proteinase 3 in patients with anti-neutrophilic cytoplasmic autoantibodies-associated systemic vasculitis in remission" Clin Exp Immunol. (available online February 28, 2003) 131(3):528-35, see Applicant's IDS of 7/24/06) in view of Ramsden et al., Blaser et al., Moses et al., and Muramatsu (Kidney International, Vol. 62 (2002), pages 1601-1610, Applicant's IDS of 10/18/04).

Matthaeus 1 teach that levels of NGAL protein are upregulated in response to experimentally induced acute ischemic renal injury in a rat model (see entire selection). By contrast, control animals displayed only minor expression of NGAL, demonstrating that renal injury and repair is associated with an upregulation of NGAL. As conveyed in the title of the article, ischemic injury can cause acute renal failure.

Similarly, Matthaeus 2 teaches that NGAL protein expression was upregulated after ischemic injury in a rat model of renal ischemia, demonstrating that upregulation of NGAL is associated with renal injury as well as repair (see entire selection). The reference further teaches that NGAL may play a critical role in the renal response to ischemic injury (last sentence).

The Matthaeus references differ from the claimed invention in that they fail to specifically teach detecting NGAL in **urine** as claimed, and in particular in urine samples taken "within…about 12 hours" in relation to the recited events.

It was well known in the art that disease processes may produce changes in the levels of certain specific analytes, and that measurement of the levels of such analytes can be used to detect the presence of the disease. This is taken to be admitted prior art because applicant has failed to traverse this assertion (see MPEP 2144.03).

Therefore, it would have been obvious to one of ordinary skill in the art detect NGAL for the purpose of diagnosing acute renal injury in light of the teachings of Matthaeus 1 or Matthaeus 2 that NGAL is specifically elevated in this disease condition, and further in view of the general knowledge of one skilled in the art that markers changed in response to disease can be used as biomarkers for diagnosis of the disease.

The Matthaeus 1 and 2 references make clear that the rat studies were performed *as an animal model of human disease* (this is made explicit in Matthaeus 2, who refer to a "rat model of renal ischemia"). , Matthaeus 1 state that the purpose of their experiment is to "further elucidate the processes involved in renal injury and repair". The findings reported therein support a "critical role in the renal response to injury" for NGAL.

Given such teachings, it would have been obvious to detect NGAL in human subjects for the clear benefit of diagnosing human disease.

In such a case, it would have been further obvious to employ urine as the sample source, rather than the kidney tissue samples examined in the rat models of Matthaeus 1 and 2, for the following reasons.

Initially, it is noted that one skilled in the art would immediately recognize that isolation of kidney tissue would be very invasive and therefore unsuitable method for diagnosing renal injury in humans.

Alternative sources of samples for biomarker detection were known in the art; specifically, it was well known to one skilled in the art of biochemical assay at the time of the invention that urine is a non-invasive and easily collected type of sample. See for example Ramsden et al., column 1, lines 15-16, which teaches that urine samples are noninvasive and convenient.

Therefore, in light of the general knowledge of one skilled in the art that urine is an easily collected and non-invasive sample source for assay of biological analytes (as taught for example by Ramsden et al.), it would have been obvious to use urine as the sample source instead of kidney tissue samples when detecting NGAL for diagnosis of ischemic renal injury in human subjects, for the advantage of being a non-invasive and easily collected sample.

One would have a reasonable expectation of success because it was known in the prior art that NGAL is excreted in urine, as taught by Blaser et al. and Moses et al.

In particular, Blaser et al. teach detection of human neutrophil lipocalin (NGAL) in urine by sandwich ELISA (see in particular the abstract; page 139, section 2.4; and pages 142-143,

sections 3.3-3.4). Moses et al. also teach that NGAL may be detected in human urine by Western Blot (Example 2 and Figure 1B).

As such, in light of the teachings of Blaser et al. and Moses et al., one skilled in the art would have a reasonable expectation of success in using urine as a sample source for detection of NGAL in response to renal injury (rather than kidney tissue as taught by Matthaeus 1 and 2) since NGAL was known at the time of the instant invention to be excreted in urine.

With respect to the combination of the Matthaeus 1 or 2, Ohlsson et al., Ramsden et al., Blaser et al., and Moses et al. references, it is noted that Ohlsson et al. adds additional evidence that NGAL was known to be elevated in the context of renal injury at the time of the instant invention.

Specifically, Ohlsson et al. teach an ELISA method to detect NGAL (p. 530, left column; p. 531, the section "PR3 versus neutrophil activation and degranulation"; Figures 3-4; and Table 4b in particular). The reference teaches the steps of obtaining a blood plasma sample from a mammalian subject; it would seem that all mammals are "at risk" of developing a renal injury as recited. However, Ohlsson et al. specifically looked at patients with ANCA-associated systemic vasculitis and recorded development of renal failure (p. 529 "Patient material"). The reference further teaches evaluating the renal tubular cell injury status based on the level of NGAL in that Ohlsson et al. teach that ***greatly elevated NGAL levels are strongly correlated with decreased renal function*** (p. 531, the left column, last paragraph). Given the broadest reasonable interpretation of "evaluating the renal tubular cell injury status", the correlating of NGAL levels with renal failure status by Ohlsson et al. meets the limitation.

Taken together with the findings of Matthaeus 1 or 2, it would have been obvious to detect NGAL for the purpose of diagnosing renal dysfunction since the references establish that NGAL is specifically elevated in this disease condition, and further in view of the general knowledge of one skilled in the art at the time of the invention that markers changed in response to disease can be used as biomarkers for diagnosis of the disease.

Although Matthaeus 1, Mattheus 2, and Ohlsson et al. did not examine NGAL levels in urine (Ohlsson et al. employed blood plasma), it would have been obvious to use urine as the sample source instead of the kidney tissue samples when detecting NGAL for diagnosis of renal injury in human subjects, for the advantage of being a non-invasive and easily collected sample (as taught by Ramsden et al.).

One would have a reasonable expectation of success because it was known in the prior art that NGAL is excreted in urine, as taught by Blaser et al. and Moses et al.

Regarding the limitation that the urine sample is obtained "within a period of time of about 12 hours after an event that is suspected of causing an acute ischemic renal tubular cell injury, and that predisposes the mammalian subject to progressing to ARF", Matthaeus 1 teach that NGAL was elevated "after 24 and 48 hours" of renal ischemia, which was induced by operation (i.e., "an event suspected of causing acute ischemic renal tubular cell injury…that predisposes the mammalian subject to progressing to ARF").

However, the references fail to specifically teach detection of NGAL in relation to one of the specific events recited in claim 1. As also discussed above, however, the references fail to specifically teach detection of NGAL "within about 12 hours" or at the specified times recited in claims 35 or 63-64.

Muramatsu et al. teach that it is imperative to diagnose acute renal failure (ARF) as soon as possible, and that disease markers that can be measured in blood or urine would be of extreme value since ARF is associated with high morbidity and mortality (see especially page 1601).

In particular, the reference teaches screening for a biomarker of ARF (Cyr61) by detecting the presence of urinary Cyr61 within specified times in relation to the onset of induced renal ischemia, as a model of ARF (see especially pages 1603-1604, "Urine Collection"; page 1606; and Figure 8). The reference exemplifies time points of 3-6, 6-9, 9-12, 12-18, and 18-24 hours after ischemia (see especially the legend to Figure 8) and report that the levels of urinary Cyr61 were seen to increase within 3-6 hours (page 1608). The reference also teaches that no urine was produced within the first three hours, such that the first time point of 3-6 hours would represent the first urine output (legend to Figure 8).

Therefore, it would have been further obvious to one of ordinary skill in the art to detect NGAL levels as early as possible as taught by Muramatsu, and in particular within the recited time ranges in relation to the onset of injury out of the normal desire of artisans to improve upon what is already known. See MPEP 2144.05. In particular, one would be motivated to detect NGAL within 24 hours or earlier in order to diagnose disease earlier, and therefore to allow for timely interventions to be performed. Given that Muramatsu exemplify time points that overlap those claimed (e.g., 3-6 hours), it would have been a matter of routine optimization to determine and select

In particular, one would be motivated to detect NGAL within 12 hours or earlier in order to diagnose disease earlier, and therefore to allow for timely interventions to be performed. One would have a reasonable expectation of success because the immunoassay method of David et al.

is more sensitive, such that upregulation of NGAL would be reasonably expected to be detectable at earlier time points than by Western blot (as performed by Matthaeus).

Muramatsu et al. further teach that the biomarker Cyr61 is rapidly induced in the kidney in response to renal ischemia, and that because of this rapid induction pattern, it may serve as an early disease marker for renal injury (see the paragraph bridging pages 1608-1609). The reference further indicates that the marker could be used in a variety of settings including after contrast administration, chemotherapy, transplantation, vascular surgery, or in kidney donors, or with multi-organ failure in the ICU.

One skilled in the art would clearly appreciate the parallels between the biomarker Cyr61 as taught by Muramatsu and the NGAL protein taught by Matthaeus 1 (and also by Ohlsson et al.). Matthaeus 1 teach that like Cyr61, NGAL is upregulated in response to renal ischemia. Taken together with the teachings of Muramatsu et al. that a marker exhibiting this property may serve as an early disease marker for renal injury after transplantation or vascular surgery, one skilled in the art would be highly motivated to employ NGAL as a biomarker of renal tubular cell injury for this same purpose. For example, it would have been obvious to detect NGAL in the context of transplantation or vascular surgery for the purpose of diagnosing ARF.

With respect to claim 5, as noted above, one would be motivated to detect NGAL in humans for the purpose of diagnosing human disease. One would have a reasonable expectation of success because Matthaeus 1 and 2 clearly indicate that detection of NGAL in rats was done as an animal model, i.e. an animal model of human disease, and further because Ohlsson et al., Moses et al. and Blaser et al. teach that NGAL is also expressed in humans. The Ohlsson et al. reference also establishes that NGAL levels in humans are correlated with renal dysfunction.

With respect to claim 33, Muramatsu exemplifies examining Cyr61 as a renal ischemic injury biomarker at time points of 3-6, 6-9, 9-12, 12-18, and 18-24 hours after ischemia (see especially the legend to Figure 8) and report that the levels of urinary Cyr61 were seen to increase within 3-6 hours (page 1608). The reference also teaches that no urine was produced within the first three hours, such that the first time point of 3-6 hours would represent the first urine output (legend to Figure 8). When taken together with the general knowledge in the art regarding the urgency of detecting ARF as early as possible, it would also have been obvious to detect urinary NGAL as a biomarker of ARF as early as possible in this same manner.

Regarding claim 61, which recites that the elevated quantity of NGAL is at least a 10-fold increase, it is noted that while the claim might suggest additional steps, none are recited or clearly required by the claim. Claim scope is not limited by such language (see MPEP 2111.04). Accordingly, the reference teachings read on the claim since this statement may be interpreted (for example) as simply describing properties of NGAL and does not require additional steps or elements. Similarly, claim 65 apparently reflects intrinsic properties of NGAL as a biomarker and does not clearly recite or require additional active method steps to be performed.

26. Claims 1, 4, 9-11, 31, 48, 55, 60, and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Matthaeus 1 or Matthaeus 2 in view of Ramsden et al., Blaser et al., Moses et al., and Muramatsu et al., or in the alternative over Matthaeus 1 or Mattheus 2 and Ohlsson et al. in view of Ramsden et al., Blaser et al., Moses et al., and Muramatsu et al. as applied to claims 5, 30, and 33 above, and further in view of David et al. (US 4,376,110).

The references are as discussed above. Matthaeus 1, Mattheus 2 and Ohlsson et al. teach that NGAL levels correlate with renal function as discussed in detail above. When taken together with the general knowledge of one skilled in the art that markers changed in response to disease conditions can be used as biomarkers for diagnosis of disease (which has been taken to be admitted prior art in the absence of a travel by Applicant of this assertion), it would have been obvious to detect NGAL levels for the purpose of diagnosing renal tubular cell injury, as discussed in detail above. It would have been further obvious to detect NGAL in urine, given that urine is a non-invasive source of sample (as taught by Ramsden et al.) and because NGAL was known to be excreted in urine (as taught by Blaser et al. and Moses et al.).

The instant claims differ from those discussed above in that they relate to antibody-based detection of NGAL, where NGAL is detected by contacting the urine sample with an antibody to NGAL and detecting the antibody-NGAL complex.

However, immunoassays, including those involving a primary "capture" antibody and secondary labeled antibody in a "sandwich" immunoassay format, were well known in the art to be sensitive and rapid means of detecting analytes in samples.

For example, David et al. teach sandwich or "two-site" immunoassays for detecting the presence of analytes in fluids, in which an unlabeled "capture" antibody is bound to a media (solid support) and then contacted with a sample containing the analyte (see in particular the abstract; column 3, line 10 to column 6, line 61, and especially column 4, lines 19-37). After formation of a capture antibody-analyte complex, a second labeled antibody is added which recognizes a different site on the analyte, resulting in the formation of a "sandwich" (see especially column 1, line 47 to column 2, lines 17; column 5, lines 45-60). This type of assay

format has great utility in detecting the presence or amount of an analyte, and the improvements reported by David et al. also produce an assay format that is rapid and sensitive while eliminating false positive results (column 8, lines 33-38; and also column 1, line 67 to column 2, line 7).

Therefore, it would have obvious to one of ordinary skill in the art to detect NGAL in the prior art methods discussed above using the well known sandwich immunoassay format, e.g. as taught by David et al. One would be motivated to employ this method to detect the presence of NGAL because it is well recognized in the prior art to be a rapid and sensitive method of detecting analytes in a fluid sample.

With respect to claims 10-11, the method of David et al. involves contacting the fluid sample with the media (solid phase) upon which the primary antibody has been immobilized (see for example column 1, lines 47-56; column 6, lines 5-17; and the Example).

Regarding claim 55, which recites that the level of antibody-NGAL complex correlates with the extent of injury, it is noted that while the claim might suggest additional steps, none are recited or clearly required by the claim. Claim scope is not limited by such language (see MPEP 2111.04). Accordingly, the reference teachings read on the claim since this statement may be interpreted (for example) as simply describing properties of NGAL and does not require additional steps or elements.

27. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Matthaeus 1 in view of Ramsden et al., Blaser et al., Moses et al., and Muramatsu et al. or in the alternative over Matthaeus 1 and Ohlsson et al. in view of Ramsden et al., Blaser et al., Moses et al. and

Muramatsu et al. as applied to claim 30 above, and further in view of either one of Valkirs et al. (US 2003/0109420 A1) or Linzer et al. (US 3,635,091).

The references are as discussed above, which teach a method for detecting NGAL in a urine sample substantially as claimed, but which fail to specifically teach that the urine sample comprises a plurality of urine samples that are obtained intermittently or continuously.

Valkirs et al. teach that one skilled in the art would recognize the value of testing multiple samples (for example, a series of samples obtained at successive time points) from the same individual, e.g. in allowing identification of changes in levels of markers over time [0107]. Such data can provide information about disease status, including appropriateness about drug therapies and identification of patient outcome.

Therefore, it would have been obvious to one of ordinary skill in the art to collect a plurality of urine samples at successive time points, i.e. intermittently as taught by Valkirs et al. in order to obtain information about renal disease status over time.

Linzer et al. teach a urine sample collector in which urine obtained by having the patient urinate continuously into the container (see especially column 1, lines 1-45 and column 2, lines 46-57). The collector separates the urine into two fractions, so that if necessary the initial urine fraction can be compared with the midstream specimen (column 2, lines 46-57). The collector can also be adapted so that the liquid can be deposited into multiple independent containers (the abstract). The reference teaches that the sample collector has the advantage in that it provides a specimen free of contamination (column 1, lines 1-73).

Therefore, it would also have been obvious to obtain multiple urine samples in a continuous fashion (continuous stream of urine) using the urine specimen collector of Linzer et al. in order to ensure that the analyzed sample was free of contamination.

28. Claims 48 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matthaeus 1 or Matthaeus 2 in view of Ramsden et al., Blaser et al., Moses et al., Muramatsu et al., and David et al., or in the alternative over Matthaeus 1 or Mattheus 2 and Ohlsson et al. in view of Ramsden et al., Blaser et al., Moses et al., Muramatsu et al., and David et al. as applied to claims 1, 31, and 46 above, and further in view of Kosako et al. (US 5,527,714).

The references discussed above fail to specifically teach the step of correlating the level of antibody-NGAL complex to the extent of the acute renal tubular cell injury that can progress to ARF.

Kosako et al. teaches antigen/antibody reactions to prepare an analyte for diagnosis, in which the level of antigen/antibody complex as measured using a detectable marker is measured. The amount of marker that is bound to the analyte (antigen) directly correlates with the amount of analyte in the sample and *becomes an index of the presence or extent of a disease* (column 1, lines 18-28).

The teachings of Kosako et al. establish that it was known to use markers of disease not only to indicate the presence of a disease but also its extent or severity.

Therefore, when taken together with the teachings of Matthaeus 1 or Matthaeus 2 which establish NGAL as a marker of acute ischemic renal injury, it would have been further obvious

to one of ordinary skill in the art to correlate NGAL levels not only with the presence of disease but with the extent or severity of disease.

29. Claim 52 is rejected under 35 U.S.C. 103(a) as being unpatentable over either Matthaeus 1 or Matthaeus 2 in view of Ramsden et al., Blaser et al., Moses et al., or in the alternative over either Matthaeus 1 or Matthaeus 2 and Ohlsson et al. in view of Ramsden et al., Blaser et al., and Moses et al. (as applied to claim 30 above), and further in view of Brady et al. (US 2002/0048779 A1).

The references discussed above fail to specify whether urine is "unprocessed" or not. Brady et al. teach assaying of biological materials including urine from a subject, in which the biological materials may be unprocessed or processed [0082].

Therefore, given that it was known to assay unprocessed urine, it would have been further obvious to one of ordinary skill in the art to provide the urine sample in unprocessed form. Motivation to use unprocessed urine would be found in the general knowledge of one skilled in the art that fewer processing steps would result in a faster, simpler method.

30. Claim 62 is rejected under 35 U.S.C. 103(a) as being unpatentable over either Matthaeus 1 or Matthaeus 2 in view of Ramsden et al., Blaser et al., Moses et al., Muramatsu et al., and David et al., or in the alternative over either Matthaeus 1 or Mattheus 2 and Ohlsson et al. in view of Ramsden et al., Blaser et al., Moses et al., Muramatsu et al. and David et al. (as applied to claim 1 above), and further in view of Brady et al.

The references discussed above fail to specify whether urine is "unprocessed" or not. Brady et al. teach assaying of biological materials including urine from a subject, in which the biological materials may be unprocessed or processed [0082].

Therefore, given that it was known to assay unprocessed urine, it would have been further obvious to one of ordinary skill in the art to provide the urine sample in unprocessed form. Motivation to use unprocessed urine would be found in the general knowledge of one skilled in the art that fewer processing steps would result in a faster, simpler method.

Double Patenting

31. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

32. Claims 1-2, 4-5, 9-11, 30-31, 33, 35, 37, 48, 52, 55, and 60-65 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over

claims 2, 4, 7-10, and 22-39 of copending Application No. 11/096,113 in view of Ramsden et al., Blaser et al., and Moses et al.

Copending application No. 11/096,113 recites a method for evaluation of a renal tubular cell injury in a mammalian subject (see especially claims 27 and 31) based on the level of NGAL in a sample. The level of NGAL may be determined by antibody binding (see claim 2), as recited in instant claim 1, for example. The sample may be taken at defined time periods in relation to the onset of a procedure or condition (see claim 35), such as coronary bypass surgery, cardiac surgery, kidney transplantation, etc. (see claim 22). For example, the sample can be obtained within 6 hours, 4 hours, 2 hours, and 30 minutes (see claim 35).

The claims of the copending application differ from the instantly claimed invention in that in application No. 11/096,113 the sample assayed for NGAL is *blood or serum* (see claims 2, 9, and 24 in particular), while the sample assayed in the instant invention is *urine.*

However, it was well known to one skilled in the art of biochemical assay at the time of the invention that urine is a non-invasive and easily collected type of sample. See for example Ramsden et al., column 1, lines 15-16, which teaches that urine samples are noninvasive and convenient. In addition, it was known in the prior art that NGAL is excreted in urine: Blaser et al. teach detection of human neutrophil lipocalin (NGAL) in urine by sandwich ELISA (see in particular the abstract; page 139, section 2.4; and pages 142-143, sections 3.3-3.4). Moses et al. also teach that NGAL may be detected in human urine by Western Blot (Example 2 and Figure 1B).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to detect NGAL in urine rather than in blood or serum for the advantages of ease of

collection associated with the non-invasive nature of urine sampling, as taught by Ramsden et al. In light of the teachings of Blaser et al. and Moses et al., one skilled in the art would have a reasonable expectation of success in using urine as a sample source for detection of NGAL in response to renal injury since NGAL was also known to be excreted in urine.

This is a provisional obviousness-type double patenting rejection.

33. Claims 1-2, 4-5, 9-11, 30-31, 33, 35, 37, 48, 52, 55, and 60-65 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30-31, 33-45, and 47-50 of copending Application No. 11/770,422 in view of David et al.

Copending Application No. 11/770,422 recites a method of diagnosing renal disorder by providing a sample of body fluid from a subject (which may be urine) and detecting the concentration of NGAL in the sample (see especially claims 30 and 45). The renal disorder may be an acute renal tubular cell injury such as acute renal failure, acute tubular necrosis, or acute tubulo-interstitial nephropathy (see claim 40). The renal injury may also be caused by a nephrotoxic agent (claim 41).

The copending application differs from the instant claims in that although it recites that NGAL can be measured by means of a specific binding molecule (claim 44), it does not specify antigen-antibody binding.

However, immunoassays involving antibodies, including those involving a primary "capture" antibody and secondary labeled antibody in a "sandwich" immunoassay format, were well known in the art to be sensitive and rapid means of detecting analytes in samples.

For example, David et al. teach sandwich or "two-site" immunoassays for detecting the presence of analytes in fluids, in which an unlabeled "capture" antibody is bound to a media (solid support) and then contacted with a sample containing the analyte (see in particular the abstract; column 3, line 10 to column 6, line 61, and especially column 4, lines 19-37). After formation of a capture antibody-analyte complex, a second labeled antibody is added which recognizes a different site on the analyte, resulting in the formation of a "sandwich" (see especially column 1, line 47 to column 2, lines 17; column 5, lines 45-60). This type of assay format has great utility in detecting the presence or amount of an analyte, and the improvements reported by David et al. also produce an assay format that is rapid and sensitive while eliminating false positive results (column 8, lines 33-38; and also column 1, line 67 to column 2, line 7).

Therefore, it would have obvious to one of ordinary skill in the art to detect NGAL in the method of the '422 application by the well known two-antibody sandwich immunoassay format, e.g. as taught by David et al. One would be motivated to employ this method to detect the presence of NGAL because it is well recognized in the prior art to be a rapid and sensitive method of detecting analytes in a fluid sample.

34. Claims 1-2, 4-5, 9-11, 30-31, 33, 35, 37, 48, 52, 55, and 60-65 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 22, 24-36, 38-42 and 44 of copending Application No. 11/770,372 in view of David et al., Ramsden et al., Blaser et al., and Moses et al.

The ‘372 application recites a method of diagnosing a renal disorder in a subject based on concentrations of NGAL in a body fluid sample (see especially claims 22 and 44). The renal disorder may be an acute renal tubular cell injury such as acute renal failure, acute tubular necrosis or acute tubulo-interstitial nephropathy (claim 32) and may be caused by a nephrotoxic agent (see claim 33).

The '372 application does not recite that NGAL is detected by antibody-NGAL complex formation. However, in light of the teachings of David et al., it would have been obvious to detect NGAL by means of a two-antibody sandwich immunoassay as discussed above.

The '372 application also fails to recite that the body sample assayed is urine.

However, in light of the teachings of Ramsden et al., Blaser et al. and Moses et al. discussed above, it would have been obvious to one of ordinary skill in the art at the time of the invention to detect NGAL in urine rather than in blood or serum (as in the ‘372 application) with a reasonable expectation of success.

35. Claims 1-2, 4-5, 9-11, 30-31, 33, 35, 37, 48, 52, 55, and 60-65 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29-30, 32-44, and 46-49 of copending Application No. 11/770,214 in view of David et al.

The ‘214 application recites a method of diagnosing renal disorder in humans by determining the concentration of NGAL in a body fluid sample (which may be urine) (see especially claims 29, 44, and 46). The renal disorder may be an acute renal tubular cell injury such as acute renal failure, acute tubular necrosis or acute tubulo-interstitial nephropathy (claim 39) and may be caused by a nephrotoxic agent (see claim 40).

The copending application differs from the instant claims in that although it recites that NGAL can be measured by means of a specific binding molecule (claim 43), it does not specify antigen-antibody binding.

The '214 application does not recite that NGAL is detected by antibody-NGAL complex formation. However, in light of the teachings of David et al., it would have been obvious to detect NGAL by means of a two-antibody sandwich immunoassay as discussed above.

36. Claims 1-2, 4-5, 9-11, 30-31, 33, 35, 37, 48, 52, 55, and 60-65 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29, 31-43, and 45-49 of copending Application No. 11/770,245 in view David et al., Ramsden et al., Blaser et al., and Moses et al.

The '245 application recites a method of diagnosing renal disorder in humans by determining the concentration of NGAL in a body fluid sample (see especially claim 29).

The copending application differs from the instant claims in that although it recites that NGAL can be measured by means of a specific binding molecule (claim 43), it does not specify antigen-antibody binding. The renal disorder may be an acute renal tubular cell injury such as acute renal failure, acute tubular necrosis or acute tubulo-interstitial nephropathy (claim 39) and may be caused by a nephrotoxic agent (see claim 40).

The '245 application does not recite that NGAL is detected by antibody-NGAL complex formation. However, in light of the teachings of David et al., it would have been obvious to detect NGAL by means of a two-antibody sandwich immunoassay as discussed above.

The '245 application also fails to recite that the body sample assayed is urine.

However, in light of the teachings of Ramsden et al., Blaser et al. and Moses et al. discussed above, it would have been obvious to one of ordinary skill in the art at the time of the invention to detect NGAL in urine rather than in blood or serum (as in the '245 application) with a reasonable expectation of success.

Response to Arguments

37. Applicant's arguments filed 6/3/08 have been fully considered.

38. Applicant's request for reconsideration of the benefit claims to prior provisional applications has been considered (Reply, page 12). However, the Examiner finds that the claims as currently amended are not entitled to the filing date of the earlier applications for reasons discussed in detail above (see ***Priority*** and the rejections under § 112, 1st paragraph, new matter).

39. With respect to the rejections of claims 5, 30, 32-33, 50 and 53 under §103(a), Applicant's arguments (Reply, pages 14-17) have been fully considered but are not persuasive.

Applicant argues for patentability on the basis of the time period in which the urine sample is obtained. The Matthaeus 1 and 2 references teach that NGAL was upregulated "after 24 and 48 hours" in relation to induction of renal ischemia. Applicant argues that the Examiner's allegation of "routine optimization" of the time of sampling does not explain what Matthaeus was attempting to optimize. See Reply, page 15, first paragraph.

This is not found persuasive because obviousness is determined in view of the sum of all of the relevant teachings in the art, not isolated teachings in the art. See In re Kuderna, 426 F.2d 385, 389 (CCPA 1970); see also In re Shuman, 361 F.2d 1008, 1012 (CCPA 1966). Appellants'

arguments focus on the teachings of the individual references, and not what the prior art as a whole would suggest to the ordinary artisan.

In the instant case, the prior art (as taught for example by Muramatsu et al.) recognized the need for early detection of biomarkers following renal ischemic injury, given the high morbidity and mortality of acute renal failure.

As to Applicant's arguments that the time periods disclosed by the Matthaeus references do not overlap those claimed, the Examiner notes that those taught by Muramatsu (e.g., 2 hours or 30 minutes after ischemia) do.

Applicant further argues that one would not reasonably expect success in detecting NGAL in urine "within 12 hours" after an event based on the findings of NGAL in tissue at 24 and 48 hours (Reply, page 15, second paragraph). However, given that other biomarkers of acute renal failure were known to be detectable in urine within 24 hours, it is maintained that one of ordinary skill in the art would have a reasonable expectation of success in detecting NGAL within 12 hours.

Applicant further argues that Matthaeus was not looking for a biomarker (Reply, page 15, third paragraph). This is not found persuasive because it was well known in the art at the time of the invention that markers changed in response to disease can be used as biomarkers for diagnosis of the disease. Therefore, when taken together with the general knowledge in the art, application of NGAL as a biomarker is suggested by the teaching of increased levels of NGAL in the context of acute ischemic renal injury by Matthaeus et al.

Applicant further points to the use of kidney tissue by Matthaeus et al., as compared to urine samples in the instant application (Reply, page 16). This is not found persuasive for

reasons of record. One of ordinary skill in the art would understand the need to perform experiments in animals as models of human disease. The Matthaeus references make clear that they are studying renal injury and repair generally. While the authors used rats as an animal model, one of ordinary skill in the art would understand the broader implications of such teachings to human renal injury and repair.

Applicant further argue that there is no reasonable expectation of success because there are thousands of proteins expressed in the kidney at any time, and yet nearly all of these proteins never appear in urine (page 16, penultimate paragraph). This is not found persuasive because NGAL was known in the prior art to be excreted in urine, as taught by Blaser et al. and Moses et al.

Applicant further argues that the cited references do not teach that the elevated quantity of NGAL detected within 12 hours of the injury-causing event can be correlated with an acute ischemic renal tubular cell injury that can progress to acute renal failure (Reply, paragraph bridging pages 16-17).

This is not found persuasive because in the instant case, the Matthaeus references teach that NGAL is elevated in the context of ischemic renal tubular cell injury, which is known to be capable of progressing to ARF (as indicated in the title of Matthaeus 1, for example). Therefore, Matthaeus does teach a correlation between NGAL levels and acute ischemic renal injury that can progress to acute renal failure.

The differences between the Matthaeus references and the claimed invention regarding sample type and time of collection are not found to serve as the basis for patentability for reasons discussed in detail above.

Applicant argues that Blaser teaches away from the claimed invention in that it describes collecting urine samples over 24 hours and then mixing them together (Reply, page 17, second full paragraph). The Examiner disagrees that such a teaching rises to the level of a teaching away; while the reference exemplifies collecting urine in this manner, it does not disparage or discourage different collection times. Indeed, in the instant specification NGAL levels were examined up to 144 hours after bypass surgery (Figure 16). When the teachings of the references are taken together with the general knowledge in the art regarding acute renal failure, and the recognized need for early detection of biomarkers following ischemic renal injury, it is maintained that it would have been obvious to assess NGAL levels as early as possible,

Regarding claim 33, Applicant argues that they believe there is no express or inherent disclosure in any one or the combination of references that disclose or suggest the feature that the first obtained urine sample is examined (Reply, page 17).

This is not found persuasive because Muramatsu exemplifies detecting a urinary biomarker of renal ischemic injury (Cyr61) at time points of 3-6, 6-9, 9-12, 12-18, and 18-24 hours after ischemia (see especially the legend to Figure 8) and report that the levels of urinary Cyr61 were seen to increase within 3-6 hours (page 1608). The reference also teaches that no urine was produced within the first three hours, such that the first time point of 3-6 hours would represent the first urine output (legend to Figure 8). Furthermore, when taken together with the general knowledge in the art regarding the urgency of detecting ARF as early as possible (as taught by Muramatsu et al.), it would also have been obvious to detect urinary NGAL as a biomarker of ARF as early as possible.

40. With respect to the rejections of 1, 4, 9-11, 31, 35, and 55 under §103(a), Applicant's arguments (Reply, pages 18-19) have been fully considered but are not persuasive. The claims differ from those discussed immediately above in that they invoke *antibody-based detection* of NGAL. Applicant does not separately argue this limitation, but argues as above that the references do not suggest sampling urine within 24 hours. Such arguments are addressed in detail immediately above.

41. Applicant does not separately argue the limitation of dependent claims 2, 48, or 55.

42. Regarding the rejection of claim 52, Applicant's arguments (Reply, pages 22-23) have been fully considered but are not persuasive. Applicant argues that a person of ordinary skill in the art would understand that the term "unprocessed" in Brady et al. refers to body samples that are homogenized. Applicant urges that the instant claims, in reciting an "unprocessed" urine sample, mean that the sample is not centrifuged. Applicant is reminded that USPTO personnel are to give the claims their broadest reasonable interpretation. The specification does not provide a specific definition of "unprocessed" that would limit this term to samples that have not been centrifuged, for example. In teaching urine as an unprocessed sample, therefore, the reference reads on the claims.

Response to Amendment

43. The Declaration filed on 6/3/08 under 37 CFR 1.131 has been considered but is ineffective to overcome the rejections under §103(a) based on the Muramatsu et al. and/or Ohlsson et al. references, for at least the following reasons.

a. ***Prior invention may not be established under this section in any country other than the United States, a NAFTA country, or a WTO member country***. See MPEP 715 . The Declaration does not indicate where the experiments described were performed, and therefore fails to establish acts performed in this country, a NAFTA country, or a WTO member country.

b. ***The Declaration is not signed by all inventors.*** An affidavit or declaration by less than all named inventors of an application is accepted where it is shown that less than all named inventors of an application invented the subject matter of the claim or claims under rejection. See MPEP 715.04. However, in the instant case, the Declaration is signed by only one of the two inventions, and no statements have been provided to indicate that signing inventor Devarajan is the sole inventor of the rejected claims. For these reasons, the Declaration is defective.

c. ***The Declaration is not commensurate with the scope of the claims.*** For example, the Declaration describes experiments performed on mice in which ischemic renal injury was induced by clamping of kidney arteries (see pages 2-3, item 7). By contrast, the instant claims relate to determination of disease in humans (see, e.g., independent claim 1) or alternatively in any mammalian subject (see claim 30). Furthermore, claim 1 indicates that the patients have undergone one of a Markush group of possible events including kidney transplantation, for example. Claim 30 recites any event suspected of causing acute ischemic renal tubular cell injury. By contrast, the Declaration only pertains to the "event" of renal artery clamping.

d. ***The Muramatsu et al. and Ohlsson et al. references qualify as prior art with 102(b) dates***. The Muramatsu reference was published in November, 2002, and the Ohlsson et al. reference was publicly available on February 28, 2003 (see the abstract of Ohlsson et al. as retrieved from the publisher's website, cited by the Examiner in the Office action mailed

5/29/07). Because the claims as currently amended are not entitled to the filing dates of the earlier provisional applications for reasons discussed above, the Declaration under § 1.131 is not effective to remove as a reference the publications by Muramatsu et al. and Ohlsson et al. since they have dates that are more than one year prior to Applicant's effective filing date.

44. Regarding the provisional double patenting rejection over co-pending Application No. 11/096,113, Applicant's arguments (Rely, page 23) have been fully considered but are not persuasive. Applicant argues that in the co-pending application, Applicants have established that NGAL in urine and in blood represent two separate and distinct pools.

This is not found persuasive for reasons of record as set forth in the previous Office action at page 42, item 55. The Examiner cannot comment on evidence filed in another case unless a copy is made of record in this one.

45. Regarding the provisional double patenting rejection over co-pending Application No. 11/770,214, Applicant's arguments (Rely, pages 24-25) have been fully considered but are not persuasive. Applicant argues that the claims of the co-pending application relate to *chronic* renal injury, while the instant claims are directed to *acute* renal injury. This is not found persuasive because claims 46 of the co-pending application recite "a renal disorder" in general, which would also encompass acute injury as explicitly recited in claim 39.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The

examiner can normally be reached on M-F 6:00-2:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641

/Long V Le/
Supervisory Patent Examiner, Art Unit 1641